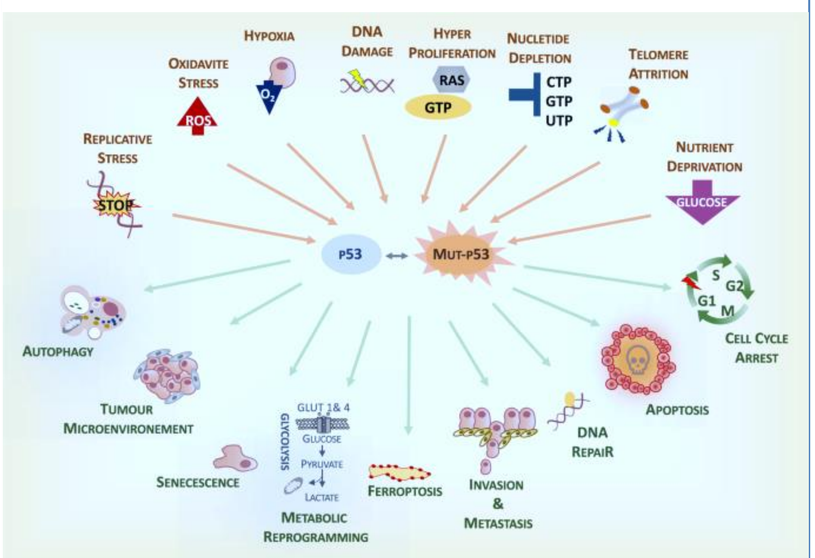
Investigating the Effects of a p53 Mutation on Glioma Progression and Therapy Resistance in *Drosophila*

Kaitlyn Alleman[3], Madhuri Kango-Singh[1,2,3]
1)Department of Biology 2) Center for Tissue Regeneration and Engineering at Dayton (TREND)
3) Premedical Programs, University of Dayton, Dayton OH 45469

Abstract

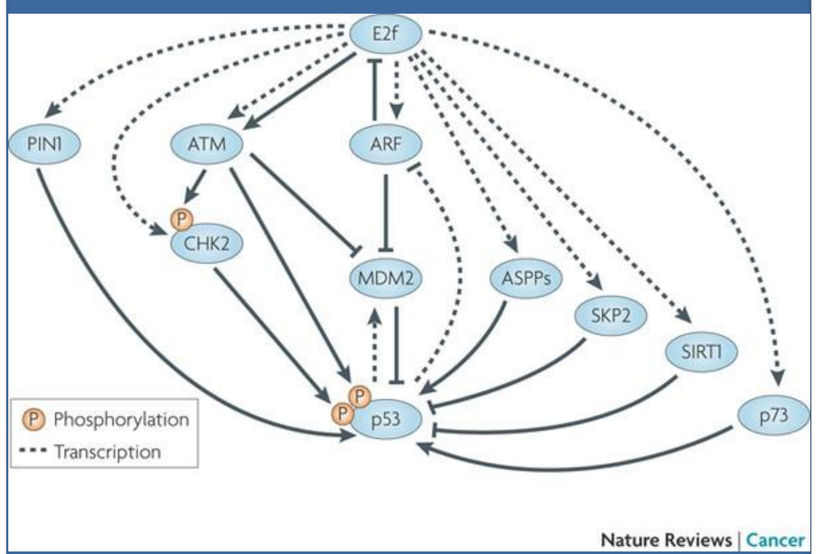
Gliomas, which are brain tumors that arise from glial cells, are some of the most aggressive and lethal types of tumors. These brain tumors are difficult to treat because not enough information regarding the mutations present in these tumors exists. This project studies effects of a p53 mutation on Drosophila glioma progression and then will test to see if this results in resistance to current chemotherapy. Drosophila are used as model organisms to mimic these processes. The current genetic crosses that have been created will be studied, and an effective p53 knockdown will be made. In essence, this will effectively mimic a human brain tumor so the treatments tested and the data collected from this model can be applied to the current understanding of human gliomas. In addition to studying just the p53 mutation, PI3K and oncogenic Ras signaling will be coactivated. This will lead to an even more accurate glioma model because multiple mutations, such as the ones added are present in human tumors as well. These genetic crosses will be treated with Tyrosine Kinase Inhibitors, which are currently used to treat brain cancer patients in order to find out whether or not this mutation plays a role in resistance to current therapy. The main goal of this endeavor is to investigate the numerous defects occurring at the cellular and biochemical level in gliomas, which will give insight into why these types of tumors are so difficult to treat. Data gathered from this project will lead to further inquiry into the role of p53 mutations in gliomas and hopefully, to better outcomes for those affected by this type of cancer. Here, we present the data gathered from this project thus far.

Role of *p53*



Cell Death Discovery

E2F Regulates *p53* Activity

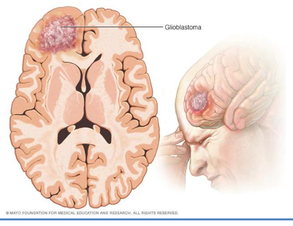


Introduction

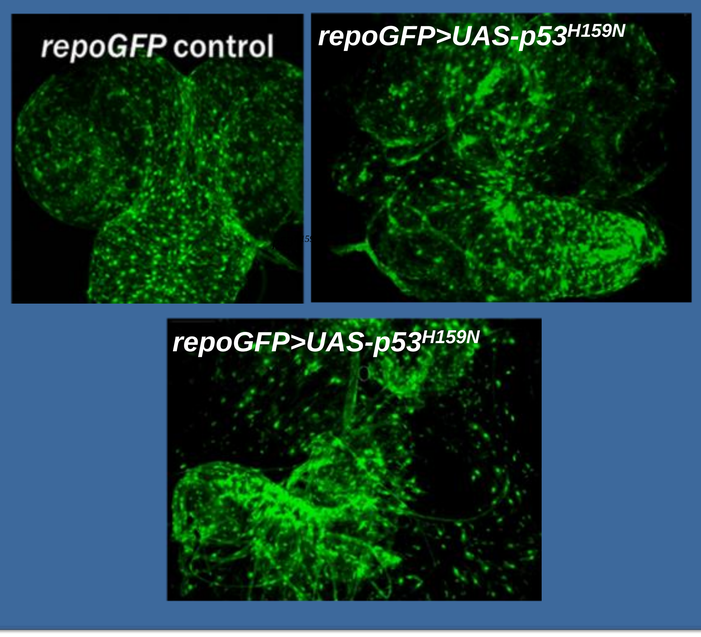
The goal of this project is to investigate why some gliomas do not respond well to chemotherapy. One approach to this is to compare the response of two genetically different glioma to a slew of drugs known to partially affect or weakly inhibit tumor growth. The p53 mutation is thought to play a role in this resistance. This specific mutation can be modeled in Drosophila melanogaster, both independently and in conjunction with other commonly occurring mutations in glioma.

The p53 gene acts as a tumor suppressor in addition to its numerous other functions concerning the cell cycle. The E2F family of genes, which will also be tested along with p53, help control the cell cycle. Mutations in both of these genes are known to occur in patients with gliomas, but their role in glioma progression and response to therapies is not well understood.

If more information regarding the exact mutations present in gliomas existed, more targeted therapies could be used to act on the pathways known to contribute to tumor development and chemotherapy resistance. This project aims to explore these mutations in an effort to bridge this gap in information, so therapies can efficiently destroy the tumor without causing damage to healthy tissues. We present the preliminary data necessary to create the various glioma model here



Loss of *p53* Causes Reduction in Glia

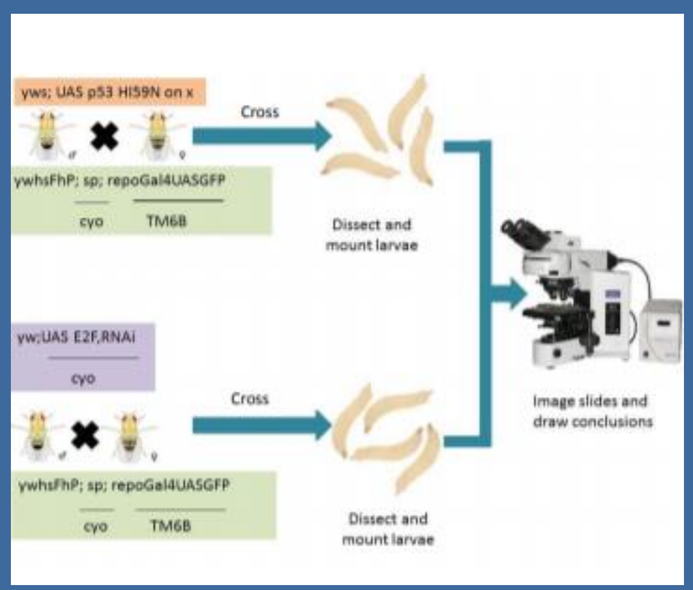


Conclusions

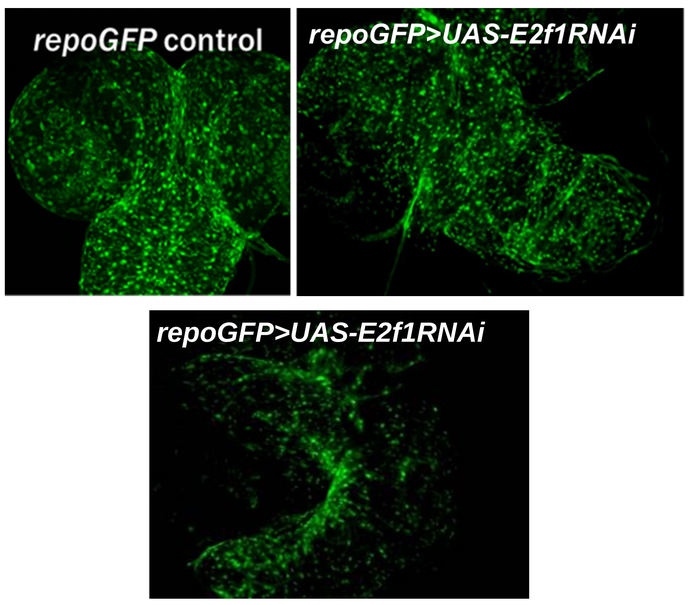
The larvae produced from the UASp53 H159N; repoGal4 cross had decreased glia in the optic lobes and they were clustered in the ventral nerve cord.

- The larvae produced from the UASE2FRNAi; repoGal4 cross had glia clustered in the ventral nerve cord as well.
- Some of the larvae from the UASE2FRNAi; repoGal4 were deformed and had their ventral nerve cord curved upward, attached to an optic lobe.
- A majority of the larvae hatched. This viability shows that further crosses made with this offspring are possible.
- This data shows promise for continued genetic crosses to eventually create a p53 knockdown which exhibits glioma.

Design



Loss of E2F Causes Reduction in Glia



Future Directions

1. Create an effective glioma model expressing a p53 mutation
2. Combine the p53 mutation with coactivation of Ras PI3 Kinase along with additional mutations that are present in human gliomas.
3. Treat the p53, Ras PI3 Kinase gliomas with Tyrosine Kinase Inhibitors in order to test for therapy resistance.
4. Use Western blotting to determine the mechanism of the mode of action.

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